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Ischemic Damage Represents the Main Risk Factor for Biliary Stricture After Liver Transplantation: A Follow-Up Study in a Danish Population

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Abstract. *Background: Biliary complications (BC) are frequently observed following liver transplantation. The aim of the present retrospective study, conducted at an outpatients' tertiary care hospital, was to determine the incidence of biliary complications and risk factors associated with their development in liver transplantation (lT) patients. Materials and Methods: The medical records were reviewed for all patients who underwent liver transplantation at the Rigshospitalet, Copenhagen, Denmark, from 2000 to 2011 and were referred to the Aarhus University Hospital for follow-up. Patients who died within 3 months of surgery or had incomplete clinical information were excluded. All data for demographic characteristics and possible risk factors for development of biliary stricture were collected. Fifty-one patients were included. Results: The median age at transplantation was 40 (range=7-64) years, and 53% of patients were males. Biliary complications occurred in 18 patients (35%), the majority of whom developed strictures (12 patients, 24%). Univariate and multivariate analyses revealed that cytomegalovirus infection (p=0.008), hepatic artery obstruction (p=0.03) and hepatic artery graft abnormalities (p=0.03) were independent risk factors for the development of biliary strictures. Conclusion: One-third of patients presented biliary complications after liver transplantation, among which biliary strictures were the most common. Cytomegalovirus infection, hepatic artery stenosis and anatomical abnormality of the graft's hepatic artery are independent risk factors for the development of biliary stricture.*

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Key Words: Liver transplantation, biliary complication, strictures, cytomegalovirus, hepatic artery stenosis.

Biliary complications (BCs) remain a major problem after liver transplantation (1, 2) and are associated with a significant burden of disease. An incidence of BC of 10-25% has been reported following liver transplantation (LT) from beating-heart donors, and even higher rates in transplantation from non-beating heart donors (3-5). Biliary stricture (BS) represents the most frequently observed post-LT biliary complication. Typically, BSs occur within the first year of LT (5-7), and the reported incidence of this type of complication reportedly ranges from 10-25% following deceased donor LT to 28-32% following living donor LT (4, 6-12). BSs are conventionally classified as anastomotic (AS) and non-anastomotic (NAS). While the development of AS is generally related to the surgical technique employed (13), the etiology of NAS is less clear. Ischemic damage is often regarded as the main cause of BS (6, 14-17). Cytomegalovirus (CMV) infection has also been reported to be associated with BS development, possibly mediated by the immunological activation induced by this infection (18).

The incidence of BCs after LT in Denmark is unknown. No previous study has identified the risk factors associated with the development of BCs in a Scandinavian population. Therefore, a study was performed on a group of patients who underwent LT in Denmark to identify incidence of BCs, risk factors associated with BS development and the impact of BCs and BS on patient survival.

Materials and Methods

The medical records were reviewed of all patients that underwent LT at Rigshospitalet in Copenhagen and were referred to Aarhus University Hospital for follow-up from 2000 to 2011. This cohort of patients was followed from the date of transplantation until biliary complication diagnosis, death, or study end (August 15, 2012). Patients who died within 3 months of LT or had incomplete clinical information were excluded. Fifty-one patients were included in this study. For transplant recipients, age, gender, body mass index, liver disease etiology, hepatitis virus B and C infection, and presence of hepatocellular carcinoma, diabetes mellitus and arterial hypertension before and after LT were analyzed; for transplant donors, age, gender and mortality due to cerebrovascular accidents were considered. Duration of operation, duration of cold and warm ischemia, type of biliary anastomosis (duct-to-duct anastomosis or hepaticojejunostomy) and presence of anatomical abnormalities of the grafted hepatic artery (HA) were also recorded. Episodes of acute rejection, CMV infection and evidence of HA obstruction (stenosis or thrombosis) were also recorded. After discharge from Rigshospitalet, all patients were followed-up at the outpatient clinic of Aarhus University Hospital.

For patients in whom cholestasis was suspected, the diagnostic approach included an abdominal ultrasound to evaluate the biliary tree and hepatic vasculature followed by a magnetic resonance cholangiopancreatography and angio-computed tomographic scan when required. In the presence of distal BS, an endoscopic retrograde cholangiopancreatography was performed with sphincterotomy and stent placement when indicated. In cases with proximal BS or endoscopic treatment failure, a percutaneous transhepatic cholangiography and stent placement was considered. Stents were changed every 3 months and permanently removed after 1 year. Treatment was defined as successful when cholangiography indicated BS resolution, cholestasis was ameliorated, and symptoms were resolved. BS was diagnosed when stenosis of the bile duct was observed on imaging in the presence of biochemical cholestasis with or without clinical symptoms. AS was diagnosed in the presence of a stenosis at the anastomotic level. Strictures, dilatations or irregularities of the intra-and extra-hepatic bile ducts, excluding the site of anastomosis, were classified as NAS.

Statistical analysis. Categorical variables are reported as the number and percentage of cases, and Pearson Chi-square and Fisher's exact tests were used for their comparisons. Continuous variables are reported as medians. Student *t*-test was used for comparing continuous variables with Gaussian distributions, while Mann–Whitney *U*-tests were adopted for variables with skewed distributions. Differences with *p*-values of less than 0.05 indicated statistical significance. Initially, univariate logistic regression analyses were performed to identify risk factors for the development of BS. Subsequent multivariate logistic regression analysis was performed including only variables with values of $p<0.1$ in the univariate analyses. Risk prediction estimates are reported as *p*-values, odds ratios (OR), and 95% confidence intervals (95% CI). Patient and graft survival rates were analyzed using the Kaplan–Meier method and compared using the log-rank test. Statistical analyses were performed and plots were generated using NCSS 2007 (NCSS, Chicago, IL, USA).

Table I. *Clinical and biochemical characteristics of the study population (n=51).*

Variable	Value
Median recipient age (range), years	40 (7-64)
Male gender, n (%)	27 (52.9%)
Liver disease etiology, n (%)	
PSC	11 (21.6%)
Amyloidosis	7 (13.7%)
Fulminant hepatitis	7 (13.7%)
Autoimmune hepatitis	5 (9.8%)
PBC	5 (9.8%)
Viral	3 (5.9%)
Alcoholic	3 (5.9%)
Other	10 (19.6%)
Acute rejection, n (%)	15 (30%)
CMV infection, n (%)	10 (20%)
Pre-LT AX, n (%)	7 (14%)
Post-LT AX, n (%)	13 (25.5%)
Pre-LT DM, n (%)	5 (9.8%)
Post-LT DM, n (%)	10 (19.6%)
Duct-to-duct anastomosis, n (%)	36 (70.6%)
Median follow-up (range), months	52.8 (3.3-147.6)

PSC, Primary sclerosing cholangitis; AX, arterial hypertension; CMV, cytomegalovirus; DM, diabetes mellitus; LT, liver transplantation.

Table II. *Types and presentations of biliary complication in study patients (n=51).*

Biliary complication	Frequency, n (%)
All biliary complications	18 (35.3%)
Stricture	15 (29.4%)
AS	6 (11.7%)
NAS	5 (9.8%)
AS and NAS	4 (7.8%)
Biloma	1 (1.9%)
Leakage	3 (5.8%)

AS: Anastomotic stricture; NAS: non-anastomotic stricture.

Results

The medical records were reviewed of 51 liver recipients with a median follow-up of 53 months. The clinical and demographic characteristics of patients are reported in Table I. For surgical team policy, none of the patients had a T-tube placed after transplantation. Biliary complications occurred in 18 patients (35.3%). The most common complications were strictures (15 patients, 29%). Of the patients with BS, six (40%) developed AS, five (33%) NAS and four (27%) both stricture types. The median time from LT to BS diagnosis was 7.8 months (range=0.1-84.2 months). In seven

Table III. *Univariate analysis of risk factors for the development of biliary stricture (BS).*

Variable	With BS (n=15)	Without BS (n=36)	*p*-Value
Recipient-related			
Recipient age (years)	40 (28-52)	43 (37-50)	0.700
Male gender, n (%)	6 (40%)	21 (51.3%)	0.200
Liver disease etiology, n (%)			
PBC	2 (13.3%)	3 (8.3%)	0.500
PSC	4 (26.7%)	7 (19.4%)	0.500
Alcohol	0	3 (8.3%)	0.300
Fulminant hepatitis	2 (13.3%)	5 (13.9%)	0.900
Autoimmune hepatitis	2 (13.3%)	3 (8.3%)	0.400
Amyloidosis	2 (13.3%)	5 (13.9%)	0.900
Viral	1 (6.8%)	2 (5.6%)	0.800
Other	2 (13.3%)	8 (22.3%)	0.300
Duct-to-duct anastomosis, n (%)	11 (73.3%)	25 (69.4%)	0.200
Episode of acute rejection, n (%)	6 (40%)	11 (30.5%)	0.600
Cytomegalovirus infection, n (%)	6 (40%)	3 (8.3%)	0.008
HAS, n (%)	6 (40%)	4 (11.1%)	0.030
Transplant performed after 2006	9 (60%)	21 (58.3%)	0.900
Duration of hospitalization (days)	30 (21-60)	21 (20-31)	0.100
Donor-related			
Median age (range), years	48.5 (38-55)	47 (36-53)	0.300
Median BMI (range), kg/m2	23.3 (21.7-26.2)	23.8 (22-26)	0.900
Mortality due to CVA, n (%)	11 (73%)	19 (53%)	0.250
Surgical-related			
Abnormalities of graft HA n (%)	4 (26.6%)	2 (5.5%)	0.030
Use of University of Wisconsin solution, n (%)	5 (33%)	11 (31%)	0.600
Median duration of biliary anastomosis packing (range), min	20 (15-35)	20 (15-26)	0.800
Hepaticojejunostomy as anastomosis	4(27%)	11(31%)	0.800
Median duration of surgery (range), h	6.50 (5.30-7.12)	6.40 (6.13-7.20)	0.500
Median duration of cold ischemia (range), h	10.50 (8.20-13)	10.46 (8-13)	0.800
Median duration of warm ischemia (range), min	55 (43-59)	52 (40-55)	0.460
Median duration of total ischemia (range), h	11.6 (8.58-14.3)	11.5 (9.38-13.5)	0.900

ALAT: Alanine aminotransferase; BAP: basic phosphatase; Bil Tot: total bilirubin; GGT: gamma-glutamyl transferase; HA(S): hepatic artery (stenosis); PBC: primary biliary cirrhosis; PSC: primary sclerosing cholangitis.

cases (47%), BS diagnosis was made within 6 months of LT, and in eight cases (53%) within 1 year. The types and presentations of biliary complications are reported in Table II. The Kaplan–Meier plot (log-rank test) showed no difference in patient or graft survival between patients with and without BSs (*p*-values of 0.9 and 0.9, respectively).

Risk factors for the development of BS. In the univariate analyses, CMV infection, HA obstruction (stenosis or thrombosis) and anatomical abnormalities of the grafted HA were associated with the development of BS. Duration of cold and warm ischemia, duration of operation, episodes of rejection and donor age were not significantly associated with the development of BS (Table III). In the multivariate analysis, CMV infection (OR=6.5; p=0.028), anatomical abnormalities of the grafted HA (OR=8.4; p=0.042) and HA obstruction (OR=7.4; p=0.048) appeared to be independent risk factors for the development of BS (Table IV).

Table IV. *Multivariate analysis (logistic regression) of significant risk factors for biliary stricture.*

Variable	OR	95% CI	*p*-Value
HA obstruction	7.4	1.16-47.35	0.048
Graft HA abnormality	8.4	1.02-72.03	0.042
CMV infection	6.5	1.01-44.9	0.028

HA: Hepatic artery; CMV cytomegalovirus; CI: confidence interval; OR: odds ratio.

Discussion

Despite continuous progress in the field of LT (19), biliary complications still affect a considerable number of LT patients (3, 4, 20). In our study, we confirmed the presence of a high BC incidence in a Danish population. Overall, 35% of LT

patients developed BCs, among which BSs were the most common, developing in 29.4% of patients. These rates were comparable with those reported in other studies conducted in similar populations (6, 7, 21, 22). However, lower rates have also been reported in some series (2, 23). These discrepancies may be explained by differences in the definitions of BCs, imaging techniques utilized for surveillance of BS and duration of follow-up (24). As also reported previously, in our series, BCs most often developed within 1 year of LT (6, 7). The development of BSs after LT has previously been reported to be associated with risk factors closely linked to ischemia, such as long ischemia time, reperfusion injury and HA thrombosis and stenosis (25-27). CMV infection and surgical technique have also previously been correlated with BS development (14, 28). In addition, recent studies have suggested that 'marginal donor characteristics' such as donor age and macrovesicular steatosis of the graft may also be important in this context (21, 29, 30).

In our study, we confirmed previous findings suggesting that HA stenosis and thrombosis were risk factors for the development of biliary strictures (31-34). Moreover, we observed a correlation between anatomical abnormalities of the grafted HA and BS development, which may also be related to ischemic damage to the biliary tree. The biliary tree may be especially vulnerable to a reduction in arterial blood flow from the HA; in fact, vascular supply to the allograft biliary system is maintained by a unique HA terminating in the peribiliary vascular plexus (16, 35, 36). The low number of included patients did not allow a separate analysis of risk factors associated with AS and NAS to be performed.

We confirmed the previously suggested association between CMV infection and BS development (14). The mechanism due to this association is likely immunological. CMV is known to be a potent up-regulator of alloantigens, thereby increasing the risk of acute rejection and chronic allograft dysfunction; these mechanisms may be linked to the development of vanishing bile duct syndrome and ductopenic rejection, leading to chronic cholestasis and, eventually, allograft failure (17, 37-40).

In contrast to the results of previous studies, we did not identify any association between the duration of warm or cold ischemia and the development of BS; neither did we observe associations between either recipient gender or age and the onset of this type of complication. However, it should be noted that the mean recipient age in our study population did not exceed 48 years. It has been suggested that the peribiliary vascular plexus is better flushed out and better preserved when low-viscosity rather than high-viscosity fluids are used (41, 42). However, to our knowledge, these observations have not yet been confirmed in randomized control trials, and in our series, no association was observed between the incidence of BS and the type of preservation fluid utilized. Moreover, the biliary anastomosis technique employed did not seem to play a role in the onset of BS; in fact, no difference was observed between patients who underwent duct-to-duct anastomosis and those who underwent a hepaticojejunostomy. Although previous studies have shown a shorter survival time in patients with BC (43), we observed no differences in patient or graft survival, which is in accordance with the findings of recent reports (21, 44, 45). Early detection of BSs and therapeutic intervention improvement in radiology or endoscopy may easily explain these results (46).

The present study has certain limitations. Firstly, it was a retrospective study, and the use of this methodology limited our ability to comprehensively collect data for all variables potentially influencing BS development, such as median blood loss and graft steatosis frequency, as these data were not available. Secondly, the small number of patients with AS and NAS prevented us from performing separate analyses focusing on these patient subgroups.

In conclusion, based on the results of our study, BSs still represent an important complication in LT patients, and the main mechanism involved in their development appears to be ischemic damage. Immunological damage mediated by CMV infection may also be involved in the onset of this complication.

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